REMARKS

Prior to this Response, Claims 2-15 and 23-36 were pending. Claims 8 and 15 were withdrawn from consideration as directed to a non-elected species. In this Response, applicants cancel Claims 2, 9-15 and 26 and amend Claim 23. The amendments do not add any new matter. The amendments to Claim 23 are supported throughout the application, as filed, for example, in original Claim 2 and on page 4, lines 19-25. Upon entry of the amendments, Claims 3-8 and 23-2-25 will be pending, with Claims 3-7 and 23-25 being under examination with respect to the elected species.

Rejection of Claims under 35 U.S.C. § 103(a)

The Examiner rejects Claims 2-7, 9-14, and 23-26 under 35 U.S.C. § 103(a) as obvious over Drabic *et al.*, *Vaccine Research* 6:67-74, 1997 ("Drabic"), in view of Karlsson *et al.*, *Microbial & Comparative Genomics*, 5:25-29, 2000 ("Karlsson"), Gray *et al. FEMS Microbiology Letters*, 215:53-56, 2002 ("Gray") and US Patent No. 6,261,568 to Gicquel *et al.* ("Gicquel"). Applicants assert that cancellation of Claims 2, 9-14 and 26 renders moot their rejection. Applicants respectfully traverse the rejection of the currently pending claims, as examined with respect to the elected species.

MPEP 2142 states: "To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at that time to that person." Applicants respectfully assert that the currently pending claims would not have been obvious to one of ordinary skill in the art in the field of the present application at the time when applicants invented the claimed embodiments of the invention. To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquires, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and

(c) resolving the level of ordinary skill in the pertinent art. *See* MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

Scope and Content of the Cited Publications and Differences with the Claims

Drabic

Drabic is a study comparing induction of protective immune responses in animal models against challenges by attenuated and virulent strains of *Francisella tularensis*. Drabic teaches the testing of immunogenic properties of three *F. tularensis* strains: (1) LVS, the only available vaccine for tularemia at the time of the study, (2) mutated LVS and (3) strain 38. Out of the three tested strains, only LVS, the known vaccine, induced protective immunity against a fully virulent tularemia strain. *See* Drabic, p. 67-68, Abstract, p. 68, Introduction, first paragraph, page 72, paragraphs 4-5. Drabic discusses the known disadvantages of LVS, which is a genetically undefined strain, on page 72, paragraph 5. The present application also discusses LVS disadvantage on page 3, lines 4-35.

In contrast to Drabic, which has merely confirmed immunogenic properties of the previously known *Francisella* vaccine, applicants identified attenuated *Francisella* strain CG57 as a strain capable of inducing protective immunity against *Francisella* infection. Applicants also found that inactivation of a gene that encodes an enzyme active early in the purine pathway, such as purF, leads to an attenuated *Francisella* strain that is capable of inducing protective immune response. *See,* for example, the present application, page 4, lines 19-25. Applicants therefore claim a method of using of an attenuated *Francisella* strain recited in the pending claims.

Drabic recognizes a problem of variability in the immunogenic properties of attenuated *Francisella* strains and concludes that "live attenuated strains of *Francisella tularensis* vary in their capabilities to induce protection against … challenge [with fully virulent *Francisella* strains]" *See* Drabic, page 68, first paragraph. Drabic suggests that "[f]uture efforts to induce effective immunity against virulent strains of *Francisella* should

focus on the induction of cellular immunity by active live immunization" and that a murine model employed in the study offers a way to select such potentially immunizing strains." *See* Drabic, page 72, last paragraph. Thus, Drabic suggests a procedure for testing potentially immunizing *Francisella* strains and identifies desired properties of such strains – they would preferably be able to induce cellular immunity. But Drabic fails to suggest any approaches to generating immunizing strains and fails to propose any underlying molecular characteristics for such strains.

Karlsson

Karlsson is a publication of the *F. tularensis* genome. Karlsson suggests that the shikimate pathway and purine metabolic pathway, both of which contain multiple genes, are potential targets for the construction of a tularemia attenuated vaccine. *See* Karlsson, page 25-26, Title and Abstract, page 36, last paragraph, page 37, first paragraph. Karlsson discusses that, in bacteria other than *Francisella*, mutations in the genes of purine pathway had variable effects on virulence and concludes that "it is clear that different pathogens have different requirements for purine precursors that can limit their ability to cause disease." *See* Karlsson, page 36, last paragraph, page 37, first paragraph.

Karlsson recognizes that, from the disclosed sequence information, "it would be difficult to predict which mutations might result in attenuated *F. tularensis* strains that could be suitable for live vaccine development." *See* Karlsson, page 37, paragraph 2. Karlsson offers very general insights into the desired properties for the potential vaccine strains, such as "a balance between reducing virulence and stimulation of a protective immune response." Karlsson fails to propose specific targets within the purine pathway that can lead to the strains possessing the desired properties. In contrast, applicants discovered that inactivation of a gene that encodes an enzyme active early in the purine pathway, such as purF, leads to an attenuated *Francisella* strain that is capable of inducing protective immune response. *See,* for example, the present application, page 4, lines 19-25. Applicants therefore claim a method of using the strain recited in the pending claims.

Gray

Gray is a study of genetic loci of *F. novicida* associated with intracellular growth. Gray teaches identification of five *F. novicida* mutants associated with poor intracellular growth *in vitro*, including CG57 strain with a mutation in a first enzyme in the purine biosynthesis pathway, purF. *See* Gray, page 53, Abstract, page 55, first column, first paragraph. Unlike the present application, Gray fails to teach administering CG57 to animals, or to suggest that CG57 could be useful for induction of protective immunity.

Gicquel

Gicquel discloses attenuated recombinant *Mycobacterium tuberculosis* and *M. bovis* BCG strains with the mutations in PurC gene of the purine pathway. Gicquel theorizes that PurC-mutated *M. tuberculosis* and *M. bovis* strains would be good tuberculosis vaccine candidates because they would stimulate potent cell-mediated immune responses. *See,* for example, Gicquel, Abstract, column 21, lines 41-55. Gicquel does not discuss or mention *Francisella* vaccines.

Gicquel teaches testing of the protective efficacy of the recombinant strains and the finding that these PurC mutants conferred similar or lower protective immunogenicity than the known tuberculosis BCG vaccine, which has variable efficacy and provides only "modest protective effect against the adult form of the disease". *See* Gicquel, column 1, lines 50-56, column 20, lines 18-28, column 21, Table 4, column 22, lines 41-54. Therefore, PurC mutations tested in Gicquel failed to generate a bacterial strain with improved protective immunogenicity, as compared to the known BCG vaccine. Naturally, Gicquel does not suggest that mutating PurC, which failed to produce improved immunogenic *Mycobaterium* strains, could predictably result in improved immunogenic strains in other bacteria.

To the contrary, Gicquel discusses various factors that may influence protective efficacies of attenuated strains, such as "the 'quality' of the cellular immune response they induce, rather than their intensity" (column 22, lines 64-65), "ability to multiply in host cells

and disseminate and persist within the host" (column 22, line 67, through column 23, line 2), and "the way an attenuated strain establishes an infection in the host, probably more than persistence in itself" (column 23, lines 12-13). Gicquel emphasizes "the difficulty encountered when using live vaccines to reach the right balance between attenuation and immunogenicity" (column 23, lines 20-22). Gicquel states that "[i]nactivating virulence genes instead of, or in addition to, "housekeeping" genes might be necessary to obtain a *M. tuberculosis* mutant which will multiply at a similar rate as BCG with the same level of attenuation." *See* Gicquel, column 23, lines 36-41.

Thus, not only does Gicquel fail to disclose an improved PurC-mutated tuberculosis vaccine and fail to suggest applying purine pathway mutagenesis approach to other bacteria, Gicquel teaches away from purine pathway mutagenesis as a predictable way of arriving at effective attenuated vaccines. In contrast, applicants discovered that, in *Francisella*, inactivation of early purine pathway metabolic genes, such as purF, in itself leads to a strain capable of conferring protective immunity against both *F. tularensis* and *F. novicida.* *See* present application, pages 25-26.

Level of One of Ordinary Skill in the Art

Based on the publications cited by the Examiner, one of ordinary skill in the art in the area of the present application might, at most, have been able to produce *Francisella* metabolic mutants. However, because multiple and complex factors contribute to immunogenicity of intracellular bacteria, such as *Francisella*, as evidenced by the publications discussed above, one of ordinary skill in the art would not have been able to predict immunogenic properties of *Francisella* purine pathway mutants.

"Obvious to Try" Rationale

In order to support a rejection under 35 U.S.C. 103, the Examiner appears to use "obvious to try" rationale. *See* MPEP 2141(III); 2143(E). To reject a claim based on this rationale, the Examiner, first, must resolve the *Graham* factual inquires. *See* MPEP 2141(II)

citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966); MPEP 2143(E). Applicants discuss above their position on the *Graham* factual inquiries.

After resolving *Graham* factual inquires, the Examiner should articulate several findings, including a finding that "there had been a number of identified, predictable potential solutions to the recognized need or problem," where "predictability is determined at the time the invention was made." *See* MPEP 2143(E) and 2143.02(III). Applicants assert that, at the time the invention was made, those of ordinary skill in the art understood that immunogenicity of attenuated bacterial strains with mutations in the genes of purine pathway depended on a complex interplay of multiple factors, including virulence and ability to persist in the cell. *See,* for example, Gicquel, column 22, line 55, through column 23, line 41; Karlsson, page 36, last paragraph, page 37, paragraphs 1-2. Applicants assert that the publications cited in the Office Action fail to support a finding that, at the time applicants invented the claimed embodiments, there were predictable solutions to the problem of identifying *Francisella* strains useful for inducing protective immunity in an animal.

In order to apply "obvious to try rationale" the Examiner should also articulate a finding that "one of ordinary skill in the art could have pursued the known potential solution with a reasonable expectation of success." *See* MPEP 2143(E). The Examiner articulates this finding on pages 6-7 of the Office Action asserting that, since (1) Karlsson taught genes in the purine pathway as potential targets for construction of an attenuated vaccine, (2) Gray constructed a purF mutant that was compromised in its ability to grow in macrophages, and (2) Gicquel constructed immunogenic attenuated *Mycobacterium* purC mutants, one of ordinary skill in the art would have had a reasonable expectation of success when attempting to combine the teachings of the cited references in order to arrive at the pending claims. Applicants respectfully disagree.

As applicants discussed, Karlsson actually teaches that purine pathway mutations lead to highly variable immunogenic properties of the attenuated strains. Gray constructed an intracellular growth-deficient purF mutant *Francisella* strain CG57, but failed to teach or

suggest that it could be used as an anti-*Francisella* vaccine. Gicquel taught that attenuation by a mutation in a purine pathway did not lead to improvements in immunogenicity over a known vaccine, which was not capable of reliably conferring protective immunity. Applicants assert that, based on at least the findings of Gicquel, one of ordinary skill in would not have had a reasonable expectation of success that mutations in the early genes of purine metabolic pathway, such as purF, would result in an attenuated *Francisella* strain capable of providing protective immunity in an animal. Applicants assert that a finding of reasonable expectation of success is unjustified based on combined teachings of the publications cited by the Examiner.

Furthermore, applicants show in the present application that a mutation in purine pathway, in itself, does not confer protective immunogenicity onto an attenuated strain. *See* present application, Example 2, beginning on page 22. *F. novicida* U112 purA mutant and CG57 purF mutants were both defective with regard to intracellular growth and virulence, but only the purF mutant strain conferred protective immunity. This additional finding further supports applicants' position that the claimed method, as a whole, would not have been obvious to a person of ordinary skill in the art at the time applicants invented the claimed compositions and methods.

In view of the foregoing, applicants respectfully assert that a combination of Drabic, Karlsson, Gicquel and Gray fails to render obvious currently pending claims, as examined with regard to the elected species or in their generic form and respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants assert that this Response is fully responsive. Based upon the remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies that may be required, or credit any overpayment, to Deposit Account Number 11-0855. If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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